



# ADIPOSE TISSUE: A MASTER IN TOXICOLOGY

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## Abstract

Conventional wisdom in the pathogenesis of obesity and related cardiometabolic, malignant and neurodegenerative diseases focuses mainly on genetic predisposition and lifestyle (high caloric foods, sedentary lifestyle, smoking). The human genome project's big promise was that it could improve our understanding of the pathogenesis and therapy of diseases. However, the genes have been found to account for only about 10% of diseases, and the remaining causes appear to be from environmental exposures, hence the exposure science emerges. Note that molecular epidemiology and toxicology may be essential partners of exposure science. Indeed, *Homo sapiens recens* is exposed to an overwhelming number of chemical contaminants circulating every day in the air, water, food, and general environment. The body is a well-equipped entity with capabilities to excrete water-soluble pollutants, but not as well-equipped to excrete some of the lipid-soluble xenobiotics. In the late 1990's, according to the European Environmental Agency more than 100 000 chemical compounds were registered in the European Catalogue of Commercialized Chemical Substances. Here we present data that adipose tissue may be an important participant in the environmental molecular toxicology. The discovery of adipocyte-secreted leptin in 1994 was a paradigm shift event in the study of adipose tissue. It was applauded by scientific community and thus triggered a new direction in the evaluation of endocrine function of adipose tissue, that is, adipoendocrinology. This is why the today's adipose tissue is viewed not merely as a lipid storage, but also as a dynamic secretory – endocrine and paracrine – organ, synthesizing, storing, and releasing a dazzling number of signaling proteins collectively termed adipokines. Numerous evidence demonstrates that the exposure to persistent organic pollutants (POP) may contribute to the pathogenesis of obesity and its related diseases. Noteworthy, these pollutants accumulate mainly in the adipose tissue. And xenobiotic-metabolizing cytochromes p450 (CYP) are expressed in adipose tissue, where CYP1A1 and CYP1B1 can bioactivate carcinogenic polycyclic aromatic hydrocarbons and xenoestrogens. Altogether, the present review highlights an adipocentric approach in molecular toxicology. It is conceptualized as adipotoxicology, that is, the study of accumulation, metabolism, and release of xenobiotics in adipose tissue in health and disease. In effect, the adipose tissue may be a new bridge between environment and health - let us call it a master in toxicology.

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*The adipose tissue in the human body is there for the best, the bad, and the worse!*

**Charles Lapiere and Erik Maquoi**  
(*Exp Dermatol* 2007; 16:67-70)

## Introduction

*Homo sapiens recens* seems to be the only species that expresses an obese phenotype (1), hence the term *Homo obesus* was recently introduced (2). Current epidemiological data show a dramatic increase in obesity globally. Alarming, similar trends are also apparent in children. Overall, obesity and related diseases are a major personal and public health concern.

The human genome project's big promise was that it could improve our understanding of the pathogenesis and therapy of diseases. However, the genes have been found to account for only about 10% of diseases, and the remaining causes appear to be from environmental exposures. Indeed, today's man is exposed to an overwhelming number of chemical contaminants every day in our air, water, food, and general environment. The body is a well-equipped to excrete water soluble pollutants, but not as well-equipped to excrete some of the lipid-soluble ones. According to the European Environmental Agency in the late 1990's more than 100 000 chemical substances were registered in the European Catalogue of Commercialized Chemical Substances. However, less is known about late toxicity effects of the majority of these compounds. There is relatively enough toxicological data for only 14% of these 100 000 substances to ensure their safety. Moreover, many fat-soluble chemicals tend to accumulate in the body's fatty tissues, where they may persist indefinitely. Thus, over 300 foreign chemicals have been identified in human adipose tissue, brain and breast milk.

Interactions between foreign chemicals (xenobiotics) and living systems occur in several phases. The first is the exposure phase where the living organism is exposed to the chemical and which may or may not be followed by uptake of the chemical into the organism. In the next phase the chemical is distributed throughout the organism. After delivery of the chemical to various parts of the organism, the next phase is metabolism mediated by enzymes, where chemical changes may or may not occur. These phases are termed "toxicokinetics," whereas the next phase is the toxicodynamic phase in which the chemical and its metabolites interact with constituents of the organism. This sequence may then be followed by a phase in which pathological or functional changes occur

Environmental toxins interfere with glucose and cholesterol metabolism, as well as with adipokine secretion, and induce

insulin resistance and cell proliferation, thus implicated in the pathogenesis of cardiometabolic and malignant diseases. Toxins are related to the development of these diseases also through multiple other mechanisms, including inflammation, oxidative stress, mitochondrial injury, altered thyroid metabolism, and impairment of food behavior.

## Adipose tissue

There are two main type of adipose tissue, white adipose tissue (WAT) and brown adipose tissue (BAT). Both are a dynamic assembly of adipocytes (fat cells), non-fat cells and extracellular matrix components. At birth, the average-size infant has approximately 5 billion adipocytes, whereas - approximately 80 billion in adult. Adding to them billions of stromal-vascular cells, makes the whole body WAT a major human's secretory organ. In humans, adipose tissue (hereafter to be considered WAT) is partitioned into two large depots (subcutaneous and visceral) and many small depots associated with heart, blood vessels, major lymph nodes, pancreas, prostate gland, ovaries, and thymus. Accordingly, two major subfields of adipobiology have emerged, adipoendocrinology (studying the endocrine activity of adipose tissue) and adipoparacrinology (studying the paracrine activity of adipose tissue); both dealing with the pathogenesis of obesity-related diseases (3-16).

The so-called "brite" (brown-in-white) adipocytes were recognized recently. These are of particular medical relevance, because current data indicate that higher amounts of brown adipose tissue are positively associated with resistance to obesity and related diseases, and that "browning" of the adipose tissue may be of therapeutic significance for these disorders (17,18).

Conventional association of the word "adipose tissue" usually refers to lipid and energy storage (white adipose tissue) and to thermogenesis (brown and "brite" adipose tissue). In white adipose tissue, however, it is much more than that.

In 1987, adipsin, a circulating serine protease of complement system, was found as the first discovered endocrine product of adipocytes. However, it was since 1994 when leptin, a circulating cytokine, was discovered which has been triggering further studies on the secretory potential of adipose tissue. Recent genomics, proteomics and microarray methodologies have dramatically increased the number of adipose tissue-secreted molecules (see Renes in this volume of *Adipobiology*), conceptually termed adipokines (3,6).

Taken together, these and other studies have shifted the paradigm of adipose tissue from simple energy storage to the body's major endocrine and paracrine organ.

## Adipose tissue as a safety or harmful xenobiotics storage site

### Safety xenobiotics site

In case of acute poisoning with different xenobiotics adipose tissue contributes to body detoxication and survival. Body distribution of different xenobiotics largely depends on their solubility in lipids or water. In this respect the quantity of a particular xenobiotic in adipose tissue will depend from its n-octanol:water partition coefficient and the ratio of lipid in adipose tissue and blood. For human this last ratio is around 200 for most environmental pollutants (19). The uptake of polychlorinated biphenyls (PCB) was directly linked to the triglyceride content of adipocytes and did not depend on the presence of caveolin-1 (20). This data set adipose tissue as the main body site for xenobiotics distribution. In a person who is obese, up to 50% of his/her weight is lipid. As a comparison, only 10% fat will be found in someone who is starving. Hence a higher dose of a particularly lipophilic drug would be needed for someone who is overweight. In some cases, storage of lipophilic chemicals in adipose tissues appears to sequester the chemicals from their toxicity target tissue, and thus obesity may be protective (21). There are few data on the distribution of war nerve agents in animal adipose tissue. Thus after whole body vapor exposure of minipigs to sarin only trace amount could be found in adipose tissue (22).

### Adipose tissue contributes considerably to overall body xenobiotics detoxication

A set of xenobiotic-metabolizing enzymes are found in adipose tissue. These include paraoxonases (human PON3) (23), carboxylesterases (24) and some isozymes of UDP-glucuronosyltransferases (25,26). Several cytochrome p450 (CYP) isozymes are also expressed in adipocytes and their activity was induced by typical lipophilic inducers: CYP 1B1 (metabolism of steroid hormones, induced by dioxin and highly expressed also in breast cancer cells); CYP 2U1 (involved in fatty acids metabolism) (27); CYP 1A1 (induced by  $\beta$ -naphthoflavone); CYP 2B's and CYP 3A's (induced by phenobarbital and dexamethasone); CYP 2E1 (induced by fasting condition) (28). Aromatase (CYP19) is also expressed in human adipose tissue and play crucial role in estrogen biosynthesis in postmenopausal women and breast cancer development (29). Downregulation of male-specific cytochrome P450 aromatase by profenofos was found (30).

### Harmful xenobiotics site

Adipose tissue is preferential depot of various lipophilic environmental pollutants, especially of those which are resistant to biological and chemical degradation, the so-called persistent or-

ganic pollutants (POP); these are also accumulated in high levels of the food chain. Thus food, especially fatty fish, meat and milk products, is the main source of human exposure to POP. The variability of the stored amount of particular POP in adipose tissue depends on dietary exposure. It is determined by adipose size and by changes in adiposity. Weight loss results in an increase of their concentration in reduced adipose tissue and their elimination rate is consequently decreased significantly with increasing body fat content.

Examples of environmental contaminants are trichloroethylene (31), alkylphenols (32), dioxins (33), polycyclic aromatic hydrocarbons (PAH) and synthetic musk compounds (SMC) (34). Recent study of Lind *et al.* (35) demonstrated that the body distribution of highly chlorinated PCB was related to the VAT/SAT ratio. In large scale epidemiological survey in women was shown that circulating concentrations of mono-isobutyl phthalate were positively related to increased fat amount in the subcutaneous abdominal region (36).

Studies show that adipose tissue stored xenobiotics can be mobilized in persons under the influences of heat exposure (rapid weight reduction in athletes), exercise, emotional stress, illness and the overnight fast during sleep. Thus they could cause some difficulty understandable pathological reactions. Some factors that could influence the response are: severity of bioaccumulation, individual sensitivities, genetic predisposition, diet and the age of patient. In some cases with organophosphate poisoning the conventional treatment caused a recurrence of symptoms attributed to mobilization of the organophosphate stored in adipose tissue (37). For instance, a case of fenitrothion poisoning promptly treated by conventional treatment caused a recurrence of symptoms attributed to mobilization of the organophosphate stored in adipose tissue (38).

When studying the reasons of sever neurotoxicity in veterans from Vietnam war, several investigators found out that it could not be attributed to defoliant exposure (so called Agent Orange) because the average level of 2,3,7,8-TCDD in their adipose tissue was not significantly different from that of the non-Vietnam veterans or the civilians (39).

Altogether, the accumulation and metabolism of environmental toxins in adipose tissue was implicated in the pathogenesis of cardiometabolic and malignant diseases. Thus, a concept of adipotoxicology and adipose tissue as "toxicrine" organ has emerged (40).

## What is that environmental obesogens?

Nowadays, the number of environmental toxicants showed as potential obesogens continuously increases. In fact, Grun and

Blumberg coined the term obesogen, in 2006 (41). These authors discovered that tin-based compounds known as organotins pre-disposed laboratory mice to gain weight. Obesogens as well as endocrine disruptors are defined functionally as chemicals (natural, pharmaceutical, or xenobiotic) that promote obesity by increasing the number and/or size of adipocytes or fat storage into the existing adipocytes (42-46).

The process by which adipose cells are derived from a mesenchymal pre-adipocyte involves an orchestrated series of differentiation steps mediated by a cascade of specific transcription factors. Of particular importance is the activation of the nuclear receptor (NR) peroxisome proliferator-activated receptor-gamma (PPAR $\gamma$ ) that heterodimers with another NR, the retinoic X receptor (RXR) and binds to specific promoter region of target genes of the pre-adipocyte and regulates its expression (47-49). By this way the PPAR $\gamma$  and RXR receptor dimer is involved in the transcriptional control of energy, lipid, and glucose homeostasis and is the main cellular target of environmental obesogens (50).

Examples of potential environmental obesogens acting mainly through activation of retinoid X receptors (RXR $\alpha$ , $\beta$ , and  $\gamma$ ) and PPAR $\gamma$  include:

**Organotins** (biocides, heat stabilisers and chemical catalysts (41,42,51) are potent nanomolar agonist ligands for the NRs RXR and PPAR $\gamma$ . *In vitro* and *in vivo* studies on animals showed that they could activate RXR/PPAR $\gamma$ -dependent pre-adipocytes gene network and regulate adipocytes number, size and function. **Polychlorinated biphenyls** (PCB) (52); **Phthalates** (53-55); **Bisphenol A** (BPA) – widely used plasticizer (56) with potent estrogen activity (57); **Polybrominated diphenyl ether** (PBDE) and **halogenated derivatives of BPA** - flame-retardants (58,59); **Dichloro-diphenyl-trichloroethane** (DDT) (60); **Butylparaben** – antimicrobial preservative in cosmetics and flavoring additive in food (61); **Phenylsulfamide family of fungicides** (Tolylfluand), used in antifouling paints as well as on fruit crops in agriculture (62); **Perfluorooctanoic acid** (PFOA) – surfactant with large industrial usage (63,64); **Heavy metals** – arsenite (65). **Drugs** – diethylstilbestrol (a synthetic form of estrogen)(66), olanzapine (atypical anti-psychotic drug), selective serotonin reuptake inhibitors, tricyclic antidepressants, the thiazolidinedione anti-diabetic drug rosiglitazone (67). In clinical trials the beneficial metabolic (anti-diabetic) effects of angiotensin type 1 receptor blocker Losartan was shown to be due to its active metabolite EXP3174 acting as partial PPAR $\gamma$  agonist (68). The body weight loss observed after the use of anticancer drug adriamycin was shown to be due to inhibition of adipogenesis by down-regulation the expression of PPAR $\gamma$  (69).

## Xenobiotics and secretion of adipokines

All PPAR $\gamma$ -activating chemicals inducing adipocyte differentiation were able to affect leptin, adiponectin, and resistin release during terminal differentiation of adipocytes, and of these the majority also induced lipid accumulation. For example, bisphenol A (BPA), at environmentally relevant doses, inhibit adiponectin and stimulate the release of inflammatory adipokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- $\alpha$ ) (70), including from breast adipose and abdominal subcutaneous adipose explants (71). Exposure to p,p'-dichlorodiphenyldichloroethylene (DDE) significantly increased the release of leptin, resistin, and adiponectin from mature adipocytes (72). Neonatal parathion exposure uncoupled serum leptin levels from their dependence on body weight, suppressed adiponectin and elevated TNF- $\alpha$  in adipose tissue (73). Long-term and low-concentration human body exposure to triclosan, an antimicrobial agent used in some toothpastes and shampoos, can inhibits adipocyte differentiation of human mesenchymal stem cells (74). Aluminum toxicity leads to an increased iron (Fe) concentration in the serum of the body. Note that high blood Fe levels causes the liver and adipose tissue to secrete hepcidin, a Fe homeostasis regulator that signals the decrease in Fe absorption by enterocytes as well as a decrease in Fe release from cellular stores such as red blood cells thus induced anemia (75).

## Environmental contaminants and prenatal and perinatal metabolic programming

The Environmental Working Group study found the average newborn has 287 chemicals in the umbilical cord blood, 217 of which are neurotoxic (76). Thus pregnant women with chronic exposure to environmental toxins are with potential risk to have obesity generation in later life (77). For example organotin exposure during prenatal adipose tissue development leads to an increased number of preadipocytes from immortal stem cells. This could correspondingly increase the steady state number of adipocytes in the adult, which could favor the development of obesity over time (78,79). Same action was find out in animals for DDT and other organochlorine compounds (60,80,81), bisphenol A (56,82,83), tributyltin (84), organophosphate pesticides (85), nicotine from maternal smoking (86) and, in general, POP (87,88). The main conclusion from these studies is that the adipocyte number is refractory to change once established in the prenatal period of developmental programming.

On important conclusion from already known facts is that although the effects of obesogens of early-life exposure are irreversible such people can reduce later harmful health effects by controlling their life style eating organic, drinking filter water,



minimize plastic in their life. As Dr Thayer stressed in the recent Workshop organized by National Institute of Environmental Health Sciences (USA) and dedicated to the problems of “Environmental Chemicals in Diabetes and Obesity”: “We were surprised at the number of chemicals that seem to be interacting with signaling pathways involved in weight regulation.” She adds that evidence also suggests these same compounds are linked to diabetes and metabolic syndrome, “an understudied but natural research direction that brings together the obesity and diabetes issues” (89).

## Conclusion

*She had never forgotten that, if you drink much from a bottle marked “poison”, it is almost certain to disagree with you, sooner or later.*

**From Alice’s Adventures in Wonderland,  
by Lewis Carroll**

Toxicology may be regarded as the science of poisons. We have provided evidence that adipose tissue may be an important participant in the environmental molecular toxicology. And conceptualized that as adipotoxicology. “Adipotoxicology” connotes the study of accumulation, metabolism, and release of xenobiotics in adipose tissue in health and disease. Accordingly, the need for human biomonitoring of xenobiotics accumulation in adipose tissue is mandatory. In effect, the adipose tissue may be a new bridge between environment and health - let us call it a master in toxicology. This holds promise in better management of the life of *Homo sapiens obesus*.

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